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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/721,042	11/21/2000	Nathaniel Hunt	3367	2319

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EXAMINER	
ZEMAN, MARY K	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 01/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/721,042	HUNT, NATHANIEL	
	Examiner	Art Unit	
	Mary K Zeman	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *16-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15 and 45-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-59 are pending in this application.. Claims 16-44 stand withdrawn from consideration. *These claims should be canceled in response to this final rejection.*

Applicant's arguments filed 10/24/03 have been fully considered but they are not completely persuasive. Any rejection not repeated below has been withdrawn.

The sequence listing, CRF, and amendments to the specification have been entered. The amendments to the claims have been entered.

The drawings were received on 10/24/03. These drawings are acceptable to the examiner.

Claims 1 and 45 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 15 and 27 of copending and commonly assigned Application No. 09/718295. Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of the instant application encompass the methods of the '295 application. Both methods require the selection of probes through the comparison of hybridization intensities. While the '295 application has additional steps that are not specifically recited in the claims of the instant application, the generic claims encompass those steps as they recite "comprising" and equivalent steps are disclosed in the specification.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. *The examiner notes Applicant's intent to defer response to this rejection.*

Claims 1-15 and 45-59 are rejected under 35 U.S.C. 102(b) as being anticipated by Hacia et al. (1998).

The claims are drawn to computer-implemeted methods for selecting probes based upon predicted hybridization intensities, and computer software products therefor.

Applicant argues that the selection of probes in Hacia et al is not for gene expression monitoring. This argument is not persuasive, as the steps set forth in the article appear to be the

same as those set forth in the claim, therefore, the probes selected would therefore be useful for gene expression monitoring. Applicant's correct notation that this article was coauthored by an inventor is not persuasive, as the inventive entity of the article is different than that of the application, and the reference date is a proper 102(b). Applicant has not provided specific arguments as to how the methods spelled out by Hacia et al. differ from those of the claims. If there is some step in Applicant's specification that would tailor the method specifically for selection of probes that are useful for gene expression monitoring, it should be inserted into the claims.

As set forth previously, Hacia et al. (Hacia, J.G. et al. Genome Research Vol 8 :1245-1258 (1998): PTO-1449) discloses computer implemented methods for selecting probes based upon predicted stability and affinity calculations which represent predicted hybridization affinity. At page 1256, the particular algorithms and equations developed are disclosed, and appear to be minor rearrangements of the equations set forth in claims 2 and 50. This algorithm predicts the potential for duplex formation between adjacent probes within a feature on the array as well as within a given probe (probe-probe interactions, and hairpin interactions). An inter- and intra-molecular probe structure normalization score is used, which takes into account perfect match and control probes, and use one of the four traditional bases as a reference base. A smooth polynomial function is employed to describe and correct for probe sequence composition effects. The correction scheme starts with finding the best least squares fit to the logs of the measured (or predicted) perfect match intensity ratios. The least squares parameters are solved using a Cholesky decomposition. These steps were all done using a computer. To the extent the claims set forth a particular method and/or steps, this disclosure anticipates the claims.

Claims 1 and 45 are rejected under 35 U.S.C. 102(e) as being anticipated by Lange et al. (USP 6,403,314 B1).

Applicant argues that Lange et al does not provide selection of candidate probes based upon intensity difference between the probes and their control probes. This argument is based on implied limitations to the term "predicting hybridization intensities" not present in the rejected claims. The claims do not specifically set forth how the intensity differences are to be measured. Lange et al provide stability predictions which are a factor in intensity of hybridization,

therefore, a comparison of the stability of the candidate and the probe would have the same result of as the comparison in the claim.

Lange et al. (USP 6,403,314 B1 having a filing date of 2/4/2000) disclose computer implemented methods of selecting probes based upon predicted hybridization. A matrix is generated that represents the ability of various probes to hybridize with the target sequence in comparison with control sequences. The term used by Lange is "stability" which is a factor in predicted hybridization intensity. The algorithms take in to account cross-hybridizations and loop formation (hairpins). The algorithms can employ free energy calculations, or other thermodynamic considerations. As such this disclosure anticipates the rejected claims.

Claims 1-15 and 45-59 are rejected under 35 U.S.C. 102(e) as being anticipated by Santalucia et al. (WO 01/94611 A2).

Applicant incorrectly states the grounds of rejection for this reference. All pending claims have been rejected over this reference. Applicant argues that Santalucia et al does not provide selection of candidate probes based upon intensity difference between the probes and their control probes. This argument is based on implied limitations to the term "predicting hybridization intensities" not present in the rejected claims. The claims do not specifically set forth how the hybridization intensities are to be measured. Further, Applicant fails to set forth any specific arguments as to how the methods of the claims differ from Santalucia.

Santalucia et al. (WO 01/94611 A2, having a priority date of 7 June 2000) discloses computer implemented methods for selecting probes *based upon predicted hybridization* between probe and target sequence. The disclosed modules of this reference appear to perform the same calculations as those recited in claims 2 and 50, however the same equations are not listed. To the extent the claims set forth a particular method and/or steps, this disclosure anticipates the claims.

Claims 1-15 and 45-59 are rejected under 35 U.S.C. 102(e) as being anticipated by Shannon et al. (US 6,251,588 B1).

Applicant incorrectly states the grounds of rejections for this reference. All pending claims have been rejected over this reference. Applicant argues that Shannon et al does not

provide selection of candidate probes based upon intensity difference between the probes and their control probes. This argument is based on implied limitations to the term "predicting hybridization intensities" not present in the rejected claims. The claims do not specifically set forth how the hybridization intensities are to be measured. Further, no specific arguments are made regarding the methods of Shannon, and how they may differ from those of the claims.

Shannon et al. (USP 6,251,588 B1 having priority to 2/10/1998) disclose methods of predicting the potential of an oligonucleotide to hybridize to a target sequence. Various parameters relating to the ability of a given sequence to hybridize to another are calculated and compared to other sequences, such as control sequences. *These parameters are indicative of a predicted hybridization intensity.* Table 1 sets forth the various algorithms employed, and they include the intramolecular partition function which is recited in a slightly rearranged form in claims 2 and 50. Various free energy equations are set forth, as well as equations to analyze probe-probe interactions, hairpin interactions sequence complexity, steric factors, etc. As such this disclosure meets the limitations of the claims.

Claims 1-15 and 45-59 are rejected under 35 U.S.C. 102(e) as being anticipated by Wolber et al. (US 6,461,816 B1).

Applicant incorrectly states the grounds of rejection for this reference. All pending claims have been rejected over this reference. Applicant argues that Wolber et al does not provide selection of candidate probes based upon intensity difference between the probes and their control probes. This argument is based on implied limitations to the term "predicting hybridization intensities" not present in the rejected claims. The claims do not specifically set forth how the hybridization intensity is to be measured. Further, no specific arguments are made regarding the methods of Wolber, and how they may differ from those of the claims.

Wolber et al. (USP 6,461,816 B1 having priority to 9 July 1999) disclose methods of predicting the potential of an oligonucleotide to hybridize to a target sequence. Various parameters relating to the ability of a given sequence to hybridize to another are calculated and compared to other sequences, such as control sequences. *These parameters are indicative of a predicted hybridization intensity.* The specification sets forth the various algorithms employed, and they include the intramolecular partition function which is recited in a slightly rearranged

form in claims 2 and 50. Various free energy equations are set forth, as well as equations to analyze probe-probe interactions, hairpin interactions sequence complexity, steric factors, etc. As such this disclosure meets the limitations of the claims.

Claims 1 and 45 are rejected under 35 U.S.C. 102(b) as being anticipated by Hyndman et al. (1996).

Applicant argues that Hyndman et al does not provide selection of candidate probes based upon intensity difference between the probes and their control probes. This argument is based on implied limitations to the term "predicting hybridization intensities" not present in the rejected claims. The claims do not specifically set forth how the hybridization intensity is to be measured. The disclosure meets the actual steps set forth in the claims

Hyndman et al. (Hyndman et al. BioTechniques (1996), 20(6), 1090-1094, 1096-1097) disclose computer simulations and predictions of hybridizations between oligonucleotide probes and a target sequence wherein *the best probes with the best predicted hybridization* are selected. The programs use several free energy calculations and meet the limitations of the rejected claims.

Claims 1 and 45 remain rejected under 35 U.S.C. 102(b) as being anticipated by Schutz et al. (1999).

Applicant incorrectly states the grounds of rejection for this art- only claims 1 and 45 are rejected. The argument that the probes selected are not for gene expression monitoring are not persuasive, as the steps of the methods are taught by Schutz, and therefore the probes would be suitable for gene expression monitoring. Applicant has not provided specific arguments as to how the methods spelled out by Schutz et al. differ from those of the claims. If there is some step in Applicant's specification that would tailor the method specifically for selection of probes that are useful for gene expression monitoring, it should be inserted into the claims.

As set forth previously, Schutz et al. (Schutz et al. BioTechniques (1999), 27(6), 1218-1220, 1222, 1224) disclose computer implemented methods of selecting oligonucleotide probes based upon predicted hybridization calculations. Control probes are employed, various free

energy calculations are used, and the program can calculate the effects of all possible mutations. As such this disclosure meets the limitations of the rejected claims.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133. In January, after the move to the new facilities, the phone number will be: (571) 272-0723.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703) 308-4028. In January, after the move to the new facilities, the phone number will be: (571) 272-0722.

The Official fax number for this Art Unit is: (703) 872-9306

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the TC1600 Receptionist whose telephone number is (703) 308-0196.

mkz
12/30/03

MARY K ZEMAN
PRIMARY EXAMINER
1631